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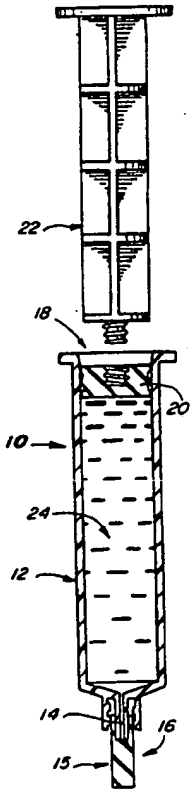
(54) Title: METHODS OF PRODUCING PREFILLED DELIVERY DEVICES WITHOUT EXTERIOR OR INTERIOR CONTAMINATION

(57) Abstract

Methods of producing prefilled, sterile delivery devices (10) without exterior or interior contamination which include preparing an assembled and sealed prefilled delivery device (10), sterilizing the assembled and sealed prefilled delivery device (10) and its contents (24), and aseptically placing the prefilled delivery device (10) in a secondary package (30) which provides a sterile barrier surrounding the delivery device (10). Optionally, the prefilled delivery device (10) can be non-aseptically placed in a secondary package (30) after sterilization and then the exterior surfaces of the delivery device (10) and the interior of the secondary package (30) can be sterilized while the delivery device (10) is in the secondary package (30). Further optionally, the prefilled delivery device (10) can be placed in a secondary package (30) prior to sterilization, thus permitting the sterilization of the exterior and interior of the delivery device (10) as well as the interior of the secondary package (30) during the initial autoclaving procedure, thereby eliminating the need for further sterilization.



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METHODS OF PRODUCING PREFILLED DELIVERY DEVICES WITHOUT EXTERIOR OR INTERIOR CONTAMINATION

Field of the Invention

The present invention relates generally to prefilled delivery devices, such as syringes, for the in vivo delivery of fluids and, more specifically, to methods of producing sterile, prefilled delivery devices without exterior or interior contamination.

Description of Prior Art

Prefilled delivery devices such as prefilled syringes are known in the art for use in various medical procedures. To produce such delivery devices, a delivery device is prefilled with the fluid to be dispensed and the entire assembly, including the delivery device and its contents, is then sterilized and supplied for end use. For example, prefilled sterile syringes of this type are disclosed in U.S. Patent Nos. 4,628,969 and 4,718,463.

While the contents and interior surfaces of such delivery devices generally remain in a sterile condition, the exterior surfaces of the delivery device may become contaminated in the process of handling by manufacturers, physicians or attending medical personnel before reaching the point of end use. The later handling of such contaminated exterior surfaces of such prefilled delivery devices by physicians who are carrying out procedures in completely sterile

environments, i.e. sterile fields, thus presents a serious risk of contamination.

Contamination of the exterior of a delivery device in an otherwise sterile environment could possibly cause serious illness, perhaps even death. Critical medical procedures are typically carried out in sterile environments to ensure that patients are not exposed to infectious agents. However, if the exterior of a delivery device were contaminated with an infectious agent and if that delivery device were used during a critical medical procedure, the likelihood that a patient would be exposed to and be infected by an infectious agent would greatly increase. An infection in a vulnerable patient undergoing such a medical procedure would clearly affect his ability to recover quickly or, perhaps, to recover at all. To date, there is no method of ensuring that both the exterior and interior of delivery devices are without contamination at the point of manufacture thereof to ensure that the introduction of infectious agents and the like into a sterile environment via a contaminated delivery device will not occur.

From the above, it is apparent that there remains a need in the art for methods of producing prefilled, sterile delivery devices without exterior or interior contamination having been sterilized at the point of manufacture and adapted for end use in a manner which avoids the risk of contamination from handling at the point of end use.

Summary of the Invention

In accordance with the present invention, methods of producing prefilled, sterile delivery devices without exterior or interior contamination are provided

which include preparing an assembled and sealed prefilled delivery device, sterilizing the assembled and sealed prefilled delivery device and its contents, and aseptically placing the prefilled delivery device in a sterile secondary package which provides a sterile barrier surrounding the delivery device. Optionally, the prefilled delivery device can be non-aseptically placed in a secondary package after sterilization and then the exterior surfaces of the delivery device and the interior of the secondary package can be sterilized while the delivery device is in the secondary package which provides a sterile barrier surrounding the delivery device. Another option would be to place the prefilled delivery device in a secondary package prior to sterilization, thus permitting the sterilization of the exterior and interior of the delivery device as well as the interior of the secondary package during the initial autoclaving procedure, thereby eliminating the need for further sterilization.

Brief Description of the Drawings

Fig. 1 is a sectional view of a prefilled sterile delivery device produced in accordance with the invention.

Fig. 2 is a sectional view of a prefilled sterile delivery device in a secondary package which provides a sterile barrier surrounding the delivery device in accordance with the invention.

Description of the Preferred Embodiments

As shown in Fig. 1, a prefilled, sterile delivery device for injecting fluid materials indicated generally at 10 and produced in accordance with one embodiment of the present invention includes a housing portion 12 having an opening or passageway 14 at one

end which is closed by a sealed tip portion 16. An open end 18 of housing portion 12 is closed and sealed by a rubber piston 20 which can be operated by a handle 22 for expelling the contents 24 through opening or passageway 14. In preferred embodiments, the housing portion 12 is produced by a suitable plastic-forming process such as injection molding of a suitable polymer such as polypropylene, or a co-polymer process of polypropylene and polyethylene. Also in preferred embodiments, sealed tip portion 16 including suitable sealing means such as a cap 15 and piston 20 may likewise be produced by injection molding a suitable elastomeric plastic or rubber material to the desired shapes.

The contents 24 can be any medicinal or diagnostic fluid material including, but not limited to, contrast media. As used herein, the term fluid means a medical fluid and encompasses liquids, gases, or combinations thereof, comprising or containing pharmaceutical media.

In a process for producing a prefilled, sterile delivery device 10 without exterior or interior contamination, a prefilled delivery device is prepared. In preferred embodiments, the prefilled delivery device is a syringe.

According to one embodiment of the present invention, the parts of the delivery device can be individually manufactured and assembled later. In this embodiment, the delivery device can be assembled and prefilled by any suitable means. For example, in U.S. Patent Nos. 4,628,969 and 4,718,463, both of which are incorporated herein by reference, the parts of the delivery device are manufactured individually, cleaned, and assembled; the assembled delivery device is prefilled; and then the piston 20 is inserted into the

open end 18 of the housing portion 12 so as to form a prefilled delivery device and to seal the fluid contents 24 in the delivery device. The assembly of the piston 20 includes the evacuation of air from the housing portion 12 via a vacuum system so that the piston 20 can be inserted within the open end 18 of the housing portion 12 with a maximum amount of oxygen-free gas above the level of the fluid contents 24.

According to another embodiment of the present invention, the housing portion 12, opening or passageway 14, and sealed tip portion 16 can be manufactured in a single unit, thus obviating the need for assembling these parts. This single unit can be prefilled and then piston 20 can be inserted into open end 18 of housing portion 12 so as to form a prefilled delivery device as described above.

According to one preferred embodiment of the present invention, after the prefilled delivery device has been prepared, the assembled and prefilled delivery device is sterilized by any suitable means. For example, the assembled and prefilled delivery device can be placed in an autoclave where the prefilled delivery device and its contents can be heated under pressure in a steam/air mixture autoclave.

After sterilization, the sterile, prefilled delivery device 10 can be aseptically handled by any suitable means including, but not limited to, handling the delivery device with sterile instruments, wearing sterile gloves and/or clothing and the like in a sterile environment, or using sterile solutions after handling the delivery device, and can be placed in any suitable sterile secondary package 30 which provides a sterile barrier surrounding the delivery device so as to provide a sterile, prefilled delivery device without

exterior or interior contamination as is depicted in Fig. 2. Examples of suitable sterile secondary packages which could provide a sterile barrier surrounding the sterile, prefilled delivery device include any suitable breathable (not airtight) or non-breathable (airtight) package which would allow and facilitate the transportation and storage of the sterile, prefilled delivery device without contamination.

According to another preferred embodiment of the present invention, after the prefilled and assembled delivery device is sterilized, the sterile, prefilled delivery device can be non-aseptically handled and placed in a secondary package 30 which provides a sterile barrier surrounding the delivery device. Examples of suitable secondary packages which could provide a sterile barrier surrounding the sterile, prefilled delivery device include any suitable breathable (not airtight) or non-breathable (airtight) package which would allow and facilitate the transportation and storage of the sterile, prefilled delivery device without contamination. At this point, the exterior surface of the prefilled delivery device and the interior of the secondary package may possibly be contaminated from the non-aseptic handling thereof, while the interior surface of the delivery device and the fluid contents therein remain in a sterile condition.

The prefilled delivery device and the secondary package 30 can then be sterilized by any suitable means so as to eliminate any contamination which might be present on the exterior surfaces of the prefilled delivery device or the interior of the secondary package 30 so as to provide a sterile delivery device

without exterior or interior contamination as is depicted in Fig. 2. Examples of suitable means for sterilizing the prefilled delivery device while it is in the secondary package include, but are not limited to, using hydrogen peroxide, electron beam irradiation, gamma irradiation, ultraviolet irradiation, ethylene oxide, ozonization, gas plasma, peracetic acid, para formaldehyde, glutaraldehyde, or beta propiolactone.

When electron beam irradiation, gamma radiation, ultraviolet radiation or any other similar agent, which can enter into the interior of the secondary package whether the package is breathable or non-breathable, is used to sterilize the delivery device and the secondary package, any suitable breathable or nonbreathable package can be used. However, when sterilization agents which require that the sterilizing agent be allowed access to the interior of the secondary package are used, only a suitable breathable package may be used as the secondary package. In this instance, the breathable package must be of such construction that it has pores or openings which are large enough to let the sterilizing agent enter into the interior of the secondary package, while the pores are also small enough to prevent contaminants, pyrogens and the like from entering into the secondary package. An example of a suitable breathable secondary package is Tyvek™ which is made by Du Pont.

Moreover, the exterior surface of the prefilled delivery device and the interior of the secondary package 30 can be sterilized by autoclaving. When sterilization of the delivery device in the secondary package 30 occurs through autoclaving, it is preferred that the secondary package 30 is made of a resinous material which can withstand the autoclaving process so

as to allow the exterior surface of the prefilled delivery device and the secondary package 30 to be sterilized under autoclaving conditions which are not severe enough to affect the amount or composition of the contents 24 of the delivery device i.e., the conditions are not severe enough to cause movement of the fluid contents 24 and/or the piston 20.

Furthermore, it is also preferred, when sterilization of the delivery device in the secondary package 30 occurs through autoclaving, that the secondary package is transparent so as to allow quick and easy quality control inspection of the sterile delivery device without exterior or interior contamination, where one of the purposes of the quality control inspection is to ensure that no substantial movement of piston 20 and/or fluid contents 24 occurred during autoclaving which would affect the volume of fluid in the delivery device.

In yet another preferred embodiment of the present invention, after the delivery device is assembled and prefilled but before the fluid contents 24 therein are sterilized, the prefilled delivery device can be non-aseptically placed in any suitable secondary package 30 which provides a sterile barrier surrounding the delivery device. The prefilled delivery device in the secondary package 30 can then be sterilized by any suitable means, such as autoclaving, so that the exterior and interior surfaces of the prefilled delivery device, the fluid contents 24 therein, and the secondary package 30 are all sterilized during the initial sterilization procedure so as to provide a sterile, prefilled delivery device without exterior or interior contamination as is depicted in Fig. 2.

Accordingly, no later sterilization procedures need to be undertaken in this embodiment.

In this embodiment, where sterilization occurs through autoclaving, it is preferred that the prefilled delivery device and the secondary package 30 are made of materials which would permit sterilization of the prefilled delivery device without allowing movement of the fluid contents 24 and/or piston 20 during the autoclaving process. It is further preferred that the secondary package 30 is also transparent for the reasons stated above.

Once the sterile, prefilled delivery device without exterior or interior contamination as is depicted in Fig. 2 is obtained by any of the methods disclosed above, this delivery device can easily be transported to the point of end use and stored in such a manner that the sterility of the delivery device can be maintained so that at the time of end use, the delivery device will be without exterior or interior contamination. That is, at the time of end use, the delivery device of the present invention can be handled by a "gloved" physician in a totally sterile environment without any contact with a possibly contaminated exterior surface of the delivery device.

As can be seen, this invention provides unique methods of producing sterile, prefilled delivery devices for injection of fluid. The combination of steps forming the methods described above is able to produce sterile, prefilled delivery devices without exterior or interior contamination which have heretofore been impossible to produce utilizing standard production procedures.

Since many variations, modifications, and changes in detail may be made to the above-described

embodiments without departing from the scope and spirit of the invention, it is intended that all matter described above and shown in the accompanying drawings be interpreted as only illustrative of one or more of many possible embodiments of the invention which is defined in the following claims.

Claims

What is claimed is:

1. A method of producing a sterile, prefilled delivery device without exterior or interior contamination comprising the steps of:

a) preparing an assembled and sealed prefilled delivery device;

b) sterilizing the assembled and sealed delivery device and its contents;

c) placing the prefilled delivery device in a secondary package which provides a sterile barrier surrounding the delivery device; and

d) sterilizing the prefilled delivery device and the interior of the secondary package while the delivery device is in the secondary package.

2. The method of claim 1, wherein said delivery device is a syringe.

3. The method of claim 1, wherein said contents of said delivery device is contrast media.

4. The method of claim 1, wherein sterilizing the assembled and sealed delivery device occurs through autoclaving.

5. The method of claim 1, wherein said delivery device in said secondary package is sterilized using hydrogen peroxide, election beam irradiation, gamma irradiation, ultraviolet irradiation, ozonization, gas plasma, peracetic acid, para formaldehyde, glutaraldehyde, beta propiolactone, or autoclaving.

6. A method of producing a sterile, prefilled delivery device without exterior or interior contamination comprising the steps of:

a) preparing an assembled and sealed prefilled delivery device;

b) placing the prefilled delivery device in a secondary package which provides a sterile barrier surrounding the delivery device; and

c) sterilizing the prefilled delivery device, the contents of the prefilled delivery device, and the interior of the secondary package while the delivery device is in the secondary package.

7. The method of claim 6, wherein said delivery device is a syringe.

8. The method of claim 6, wherein said contents of said delivery device is contrast media.

9. The method of claim 6, wherein sterilizing the assembled and sealed delivery device occurs through autoclaving.

10. A method of producing a sterile, prefilled delivery device without exterior or interior contamination comprising the steps of:

a) preparing an assembled and sealed prefilled delivery device;

b) sterilizing the assembled and sealed delivery device and its contents; and

c) aseptically placing the prefilled delivery device in a sterile secondary package which provides a sterile barrier surrounding the delivery device.

11. The method of claim 10, wherein said delivery device is a syringe.

12. The method of claim 10, wherein said contents of said delivery device is contrast media.

13. The method of claim 10, wherein sterilizing the assembled and sealed delivery device occurs through autoclaving.

14. A prefilled, sterile delivery device without exterior or interior contamination produced according to the method of claim 1.

15. A prefilled, sterile delivery device without exterior or interior contamination produced according to the method of claim 6.

16. A prefilled, sterile delivery device without exterior or interior contamination produced according to the method of claim 10.

17. A prefilled, sterile delivery device without exterior or interior contamination, comprising:

a) a prefilled delivery device; and

b) a secondary package, wherein said prefilled delivery device is placed in said secondary package such that said secondary package provides a sterile barrier surrounding said delivery device.

18. The delivery device of claim 17, wherein said delivery device is a syringe.

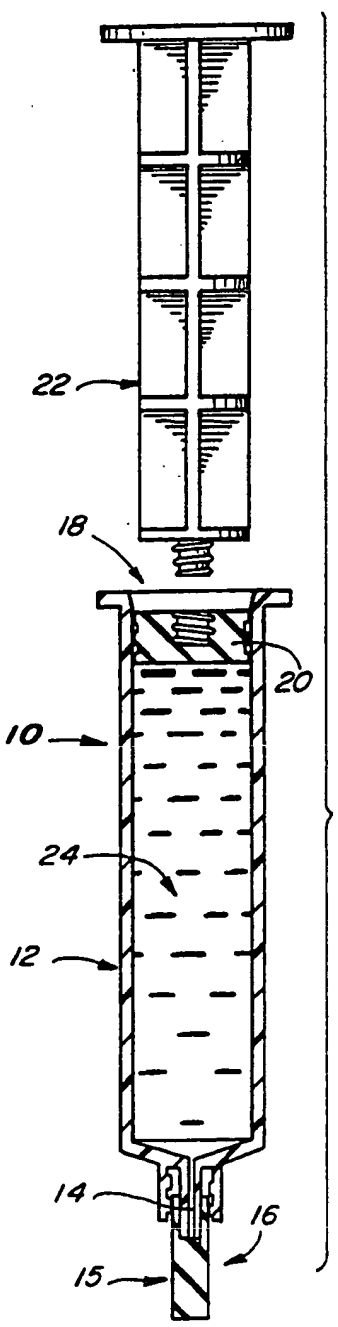

Fig. 1

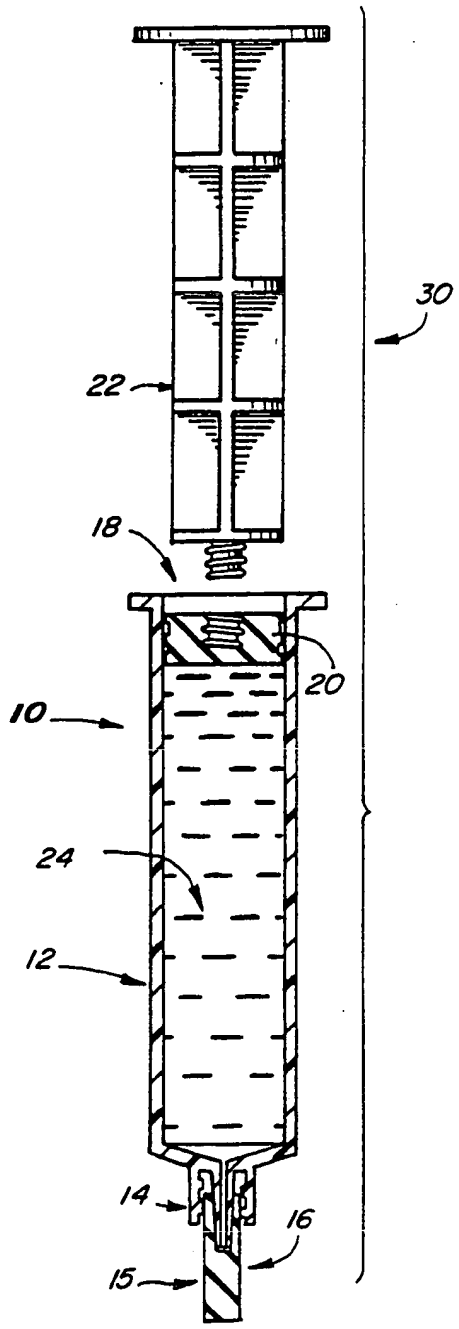

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11959

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61L 2/00; B65B 55/00; B65D 85/00; A61L 17/00
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 53/425, 449; 206/63.3, 205, 438; 422/1, 21, 22, 25, 28, 302; 426/124, 399, 401, 407, 412

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 4,878,903 (Mueller) 07 November 1989, col. 2, lines 19-22.	6-8,15,17,18 9
Y	US, A, 5,031,762 (Heacox) 16 July 1991, col. 1, lines 65-68 and col. 2, lines 1-60.	1-5, 10-14, 16
Y	US, A, 4,628,969 (Jurgens, Jr. et al) 16 December 1986, col. 1, lines 15-35.	1-5, 10-14, 16
A	US, A, 5,033,252 (Carter) 23 July 1991, col. 4, lines 10-43.	5
A	US, A, 3,891,779 (Robinson) 24 June 1975, col. 13, lines 43-60.	10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER:
US CL: 53/425, 449; 206/63.3, 205, 438; 422/1, 21, 22, 25, 28, 302; 426/124, 399, 401, 407, 412